

REMARKS

Reconsideration is requested.

Claims 1-74, 76-78 and 80 have been canceled, without prejudice, to advance prosecution.

The recitation of the claimed complements have been revised to recite the specific sequences, and claim 81 has been amended to recite the specific sequences which were part of the claims from which the unamended claim depended. Claims 86 and 87 have been amended to further identify the recited type- and subtype-specific amino acid residues. Claims 86 and 87 recite the inclusion of at least 12 contiguous nucleotides, which finds support, for example, at page 8, line 2, of the specification. No new matter has been added. The amendments are not believed to raise new issues requiring further search and/or consideration. New claims have not been added. Entry of the claims will, at a minimum, reduce the issues for appeal, as described below. Entry of the amendments is requested.

The Examiner is again requested to return a completely initialed copy of page 1 of PTO 1449 Forms which were filed May 4, 2001, and of which a partially initialed copy was received with the Office Action of October 6, 2003. Specifically, the Examiner has executed the entirety of the Form and included her initials in the column to the left of the listed "U.S. Patent Documents" and "Foreign Patent Documents". The Examiner has not however included her initials in the left column next to the listed "Other Documents". The applicants last made a similar request on September 2, 2004 and included a copy of the previously-received PTO 1449 Form for the Examiner's information. Return of a completely initialed copy of the PTO 1449 Form is requested.

Claims 75, 79 and 81-87 are pending. Upon entry of the present Amendment, claims 75, 79, and 81-87 will be pending.

The Section 112, second paragraph, rejection of Claims 75, 79 and 81-87 is obviated by the above amendments. Entry of the present Amendment will, at a minimum, reduce this issue for appeal. The amended claims do not refer to the previously objected-to "at least 5 nucleotide" although the applicants believe the unamended claims are definite in this regard. Moreover, the claims have been amended to refer to "the" complement of specific sequences, which is believed to obviate the Examiner's concerns regarding the recitations of complements in the unamended claims.

The Examiner is urged to appreciate that the nucleotides encoding the amino acids recited in claim 86 and 87 are not "random ... polynucleotide primers" as suggested by the Examiner on page 2 of the Office Action dated April 11, 2005. Rather, the recited amino acids were identified as amino acids unique to the claimed HCV sequences and which are not present in any of the amino acid sequences identified prior to the filing of the priority application. The identification of the recited amino acids involved alignment of multiple HCV amino acid sequences, including sequences of the art, and screening for amino acids present in the HCV sequences of the present invention but not present in prior published HCV sequences. See, Figures 2, 4 and 6 of the present application.

The recited "12 contiguous nucleotides" will be understood by one of ordinary skill in the art to require, regardless of the reading frame, a fragment of at least 3 consecutive amino acid sequences, of which there is one of those specified in claims 86

and 87. The remaining nucleotides encoding the additional at least 2 amino acids are also not random as they are (i) part of a sequence encoding a HCV polyprotein and (ii) occur at a specified position in the HCV sequence relative to the sequence encoding the amino acid specified in claims 86 and 87 (i.e., at least 12 contiguous nucleotides).

The at least 3 (and up to at least 4) amino acids encoded by the polynucleic acids of claims 86 and 87 are necessarily encoding a part of at least 3 (and up to at least 4) consecutive amino acids of an HCV polyprotein of which at least 1 amino acid is unique to the HCV type or subtype as specified in claims 86 and 87. There is the possibility of 2 consecutive or non-consecutive amino acids unique to a given HCV type or subtype in the same fragment, e.g., V2652 and Q2653 for HCV type 7, or Q2752 and D2754 of HCV type 11.

The claims are submitted to be definite. Entry of the above and withdrawal of the Section 112, second paragraph, rejection of claims 75, 79 and 86-87 are requested.

The Section 112, first paragraph "written description", rejection of claims 86 and 87 "and claims 81-85 in as far as they read on [sic, depend from ?] claims 86 and 87" is obviated by the above amendments which have been made in response to the Examiner's statement on page 3 of the Office Action dated April 11, 2005, that "Claims directed to these specific SEQ ID NO's [SEQ ID NO: 1, 3, 5 etc. odd numbers to 105, and sequences encoding SEQ ID NO:107-207 which correspond to specific portions of HCV genomic sequences that fall within certain subtypes] would meet the written description provisions of 35 USC 112, first paragraph." Moreover, as the Examiner has apparently based, at least in part, the Section 112, first paragraph, rejection on the alleged indefiniteness of claims 86 and 87 (see, page 2, last paragraph, of the Office

Action dated April 11, 2005), and the Section 112, second paragraph, rejection has been obviated by the above, withdrawal of the Section 112, first paragraph, rejection is requested.

Entry of the present Amendment and withdrawal of Section 112, first paragraph "written description", rejection of claims 81-87 are requested.

The Section 102 rejection of claims 81-87 over Houghton (U.S. Patent No. 5,350,671) is obviated by the above amendments. The amended claims do not refer to the "short polynucleotide sequences" which are believed to have been the basis for the rejection. See, page 3 of the Office Action dated April 11, 2005.

Attached is a 24 page comparison of relevant parts of the sequence of Figure 66 of the cited Houghton et al reference as compared with Figures 2, 4 and 6 of the present application. The attached further illustrates that the sequence of Houghton et al is identical to the HCV sequence occurring on top of each of the applicants sequence alignments. The Examiner will also appreciate that for the NS5B region, the amino acid numbering of Houghton et al differs with 1 integer from the amino acid numbering in Figure 6 of the present application. That is, for example, in claim 86, S2645 is listed as an amino acid unique to type 7, whereas the closest S in the NS5B sequence is Houghton is at position 2646. The numbering of the claims has been clarified by reference to Figures 2, 4 and 6.

Entry of the present Amendment and withdrawal of the Section 102 rejection are requested.

Maertens et al
Appl. No. 08/836,075
Monday, June 11, 2005

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

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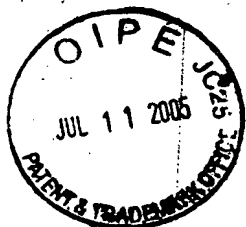


FIG.66A

R T

MSTNPKPQKKNKRNTRRPQDVKEFGGGQIVGGVYLLPRRGPRLGVRATR

1 MSTNPKPQKKNKRNTRRPQDVKEFGGGQIVGGVYLLPRRGPRLGVRATR 50

1a -----R-T-----

1b -----R-T-----

1d -----R-T-----XXXXX-----X-----

1d -----R-T-----X-----

1e -----R-T-----V-----A-----

1f -----R-T-----

HCJ6 2a -----R-T-----

HCJ8 2b -----R-T-----

CH610 2c -----R-T-----

NE92 2d -----R-T-----

BNL3 2e -----R-T-----

FR4 2f -----R-T-----

HCVTR 3b ---L---RQT---L---N---V---V---

DK13 4d -----R-T-----M-----

CAM600 4e -----R-T-----M-----

GB809 4e ---L-R-T---M-----

BNL7 4k -----R-T-----M-----

BE95 5a -----R-T-----M-----

HK2 6a ---L---R-T---T-----

FR1 7a ---L---R-T---M-----

VN4 8a ---L---R-T---I-----

VN13 8b ---L---R-T-----

VN12 9a ---L---R-T---M-----

NE98 10a ---L---R-T---X---V---Q---V---

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Figure 2 - continued

		KT S E R S Q P R G R R Q I P K A R R P E G R T W A Q P G Y P W P L Y G N E G C G W A G W L L S P - 100	
		51	100
HCV1	1a	K T S E R S Q P R G R R Q I P K A R R P E G R T W A Q P G Y P W P L Y G N E G C G W A G W L L S P	
HCV-J	1b	-----M-----	
BNL1	1d	-----X-X--S-----X-----	
BNL2	1d	-----D-----QSD-XX-----H-----	
CAM1078	1e	-----E-----	
FR2	1f	-----S-----A-----	
HCV6	2a	-----D--ST-KS-GK-----L-----	
HCV8	2b	-----D--ST-KS-GK-----	
CH610	2c	-----D--TT-KS-GR-----L-----	
NE92	2d	-----D--T-KS-GK-----L-----	
BNL3	2e	-----D-XAT--S-GR-----L-----	
FR4	2f	-----D--AT-KS-GR-----L-----	
HCVTR	3b	-----KQ-HL-----SR--S-----K--L-----	
DK13	4d	-----QL--S-----	
CAM600	4e	-----T--S-----	
GB809	4e	-----S--S-----	
BNL7	4k	-----S--S-----X-----	
BE95	5a	-----Q-T-S-G-----A--L-----	
HK2	6a	-----Q-Q-H-----	
FR1	7a	-----V-Q-T-S-G-----	
VN4	8a	-----V-HQT-----	
VN13	8b	-----V-HQT-----	
VN12	9a	-----A-----V-QNQ-----	
NE98	10a	-----S-----R--T--S-----	

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Figure 2 - continued

		RGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARA	
		101	150
HCV1	1a	RGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARA	
HCV-J	1b	-----	
BNL1	1d	-----N-----	
BNL2	1d	-----	
FR2	1f	-----N-----S-T	
HC-J6	2a	-----N-H-V-----V-V-	
HC-J8	2b	-----T-H-R-I-----V-V-V-	
CH610	2c	-----H-----V-V-V-	
NE92	2d	-----H-----V-V-V-	
BNL3	2e	-----XX-X-V-V-X-	
FR4	2f	-----N-H-X-V-V-V-	
HCV-TR	3b	-----N-F-----V-V-	
GB116	4c	-----V-V-	
DK13	4d	-----N-----V-V-V-	
CAM600	4e	-X-X-N-X-----V-V-	
GB809	4e	-----N-----V-V-	
G22	4f	-----V-V-	
GB549	4g	-----V-V-	
GB438	4h	-----V-V-	
BNL7	4k	-----N-----	
BE95	5a	-----N-N-K-----G-I-V-	
HK2	6a	-----H-N-----V-V-A-	
FR1	7a	-----N-N-----XXL-VL-G-V-A-	
VN4	8a	-----N-N-----V-X-V-X-	
VN13	8b	X-N-N-X-----XX-IE--	
VN12	9a	-----D-X-N-X-----E-V-V-AE	
NE98	10a	-----N-----	

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Figure 2 - conti

		LAHGVRVLEDGVNYATGNLPGCSFSIFLLALLSCLTVPASAYQVRNSTGL-200	
		151	200
HCV1	1a	LAHGVRVLEDGVNYATGNLPGCSFSIFLLALLSCLTVPASAYQVRNSTGL	
HCV-J	1b	-----I-----E---VS-I	
BNL1	1d	-----XT-HE---AS-V	
BNL2	1d	-----F-----TT-HE---AS-V	
FR2	1f	-X-----XG-XXXXX-X--XX--X-----T--E-HST-DG	
HC-J6	2a	-----F-----I-T-V--AE-K-ISTG	
HC-J8	2b	-----I-----V--V--VE---ISSS	
CH610	2c	-----I-----S-----IS--V--VE-K-TSTS	
NE92	2d	-----I-----I-----V--GL--K-TSSS	
BNL3	2e	-X-----I--X-----X--V--V-XVE-K-TSQA	
FR4	2f	-----I-----I-----V--I--K-NSHF	
BNL4	2g	-----V--V--K-TSTM	
BNL5	2h	-I-----V--K-TSHS	
BNL6	2i	-I-----I--V--V--A-RS-S	
HCV-TR	3b	-----A-G-----F---C---GLEYT-TS--	
GB116	4c	-E---AV---I-----S-----T--VNY--AS-V	
DK13	4d	-----L-----NY---S-V	
CAM600	4e	-----AV---I-----T--VNY--AS-I	
GB809	4e	-----AV---I-----GVNY--AS-V	
G22	4f	-----AV---I-----VHYH-TS-I	
GB549	4g	-----AV---I-----QHY--IS-I	
GB438	4h	-----AV---I-----V--R-----QHY--AS-I	
BNL7	4k	--I-F-----IN--VS-I	
BNL8	4k	--I-----IN--VS-I	
BNL9	4k	--I-----IN--VS-I	
BNL9	4k	--I-----I--X--X-----TNY--VS-I	
BNL10	4k	--I-----X-----TNY--VS-I	
BNL11	4l	--I-----I-----QHY--VS-I	
BE95	5a	-----I-----VPY--AS-I	
HK2	6a	-----AI---I-----T---LTYG--S--	
FR1	7a	-----AI-----T---I--K-AS-I	
VN4	8a	-----XXI--X-----X--XX-X--X-----T---AHYT-KS--	
VN12	9a	-X---AI---I-----X-----T---LNYA-KS--	
NE98	10a	--I-F-----F---LT-TAGLEY--AS--	

Figure 2 - continued

		YHVTNDPCNSSIVYEAADAILHTPGCVPCVREGNASRCWVAMTPTVATRD	
		201	250
HCV-1	1a	YHVTNDPCNSSIVYEAADAILHTPGCVPCVREGNASRCWVAMTPTVATRD	
HCV-J	1b	-----S-----M-M-----S-F-----L---L-A-N	
BNL1	1d	-----S---I---MDGM-M-Y-----D-HL---M-L---L-VKX	
BNL2	1d	--L---S---I---MSGM---A-----N-S---MXL---L-VK-	
FR2	1f	-----S-G-----K-I-----X---I---I-----PL---L-A-I	
HC-J6	2a	-M-----T-D--TWOLQA-V-V-----EKV--T---IPVS-N--VQO	
HC-J8	2b	-YA---S-N--TWOLT-V-L-----ENDNGTLH--IQV--N--VKH	
CH610	2c	-M-----S-----WOLEG-V-----EQI-----FVS-N--I-Q	
NE92	2d	-M-----Q---WQLR-V-V-----EEK--I---IPVS-NI-VSQ	
BNL3	2e	-MA---S-N--WQLX-V-V-----ENSSGRFH--IPIS-NI-VSK	
FR4	2f	-MA---A-D--WQLR-V-V-----E-S--RTF--T-VS-N--VSR	
BNL4	2g	-MA---S-N--IWOMOG-V-V-----ELQ--K---IPV--N--VNO	
BNL5	2h	-M-----S---WQLK-V-V-----E-HQ-Q---IPV--N--VSQ	
BNL6	2i	-M-----S---WOLEE-V-V-----EWKD-T---IPV--NI-VSQ	
HCVTR	3b	-VL---S-G-----E-V--L-----TT--Q-S--TTVST---V-T	
GB116	4c	--I-----D-YH--L--L---V-Q-----L---APY	
DK13	4d	-----TDYH--L-----K-T--SL---AQH	
CAM600	4e	--I---A---TENH--L-----T-Q-----L---SPY	
GB809	4e	--I---A---TDNH--L-----KT-Q-----L---SPY	
G22	4f	--L-----F--VHH--L-----T-Q-----L---L-APY	
GB549	4g	-----DHH-M-L-----T-T---PL---APY	
GB438	4h	-----DHH-M-L-----T-V---IPL---VPY	
BNL7	4k	-Y-----DHH--L-----Q-----L---APY	
BNL8	4k	-----DHH--L-----T-Q-----L---APY	
BNL9	4k	--I-----DHH--L-----V-Q-S---L---I-APY	
BNL9	4k	-----DHH--AL-----V-Q-----L---APY	
BNL10	4k	-----F--DHH--L-----K--H---L---APY	
BNL11	4l	-----SDHH--L-----KT--T---L---API	
GB724	4x	--I---V---TDHH--L-----T-V---TPV---AVS	
BE95	5a	-----DNL--A-----MT--V-----QI---LSAPS	
HK2	6a	--L-----L--DAM--L--L---VDDR-T--H-V---L-IPN	
FR1	7a	--L---S-N--F--ETM--L-----IKA--E---LPVS--L-VPN	
VN4	8a	--L-----ETL--L-----KXX-Q-----QAS--L-VPN	
VN12	9a	--L-----NGM--L-----KT--LTK--LSAS--L-VQN	
NE98	10a	-M-----S-G-----G-I--L-----S--T---IPVSX---VKS	

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Figure 2 - continued

		GKLPATQLRRHIDLLVGSATLCSALYVGDL CGSVFLVGQLFTFSPRRHWT-300
		251
HCV-1	1a	GKLPATQLRRHIDLLVGSATLCSALYVGDL CGSVFLVGQLFTFSPRRHWT
HCV-J	1b	SSI-T-TI---V---A-A---M---S---YE-
BNL1	1d	ASV-TXAI---V---XX-F---M-X---A---M-H-
BNL2	1d	ANV-TAAI---V---T-AFR-M---LYH-
FR2	1f	ANA-IDEV---V---A-VF---M-I---G---TS-
HC-J6	2a	PGALTQG--T---MV-M---G-M-AA-M-IV--QH--F
HC-J8	2b	RGALTRS--T-V-MI-MA--A---V--A-MILS-A-MV--Q--NF
CH610	2c	PGTLTKG--A-V-VI-M---V--ALMIAA-AVIA--Q--TF
NE92	2d	PGALTKG--T---TIIA---F---I---A-M-AS-V-II--QH-KF
BNL3	2e	PGALTKG--AR--AV-M---V--A-MIAA-A-IVA-K--YF
FR4	2f	PGALTRG--A---TI-M---I---A-MIAA-VAVV--QY-TF
BNL4	2g	PGALTRG--T---TI-MV---I--V--A-MIAA-VVIV--QH-NF
BNL5	2h	PGALTRG--T---TI-A--V---F--A-M--S-F-MI--QH-IF
BNL6	2i	PGAXTKG--T---II-A---F-----
HCVTR	3b	LGVTIASI-T-V-M---ARQ-----AF-A-----A--R---T-
GB116	4c	VGA-LES--S-V-M--A--V-----I---G-----M-S-Q-----
DK13	4d	LNA-LES---V-M-G-----I--V-G-----Q-----
CAM600	4e	AGA-LEP---V-M-A-M-----I---GL-----M--Q-----
GB809	4e	VGA-LEP---V-M-A-V-----GL-----M--Q-----
G22	4f	LGA-LESM---V-M-T-----GI--A-M--R--L---
GB549	4g	VGA-LESM---V-M-A-V-----I---G-----M--R-----
GB438	4h	LGA-L-SV-Q-V-M-A-----I--H--G--A-MVS-Q-----
BNL7	4k	IGA-LES--S-V-M-A--V-----I--X-XGL-----M-S-R-----
BNL8	4k	IGA-LES--S-V-M-A--V-----I---GL-----M-S-R-----
BNL9	4k	IGA-LES--S-V-M-A--V-----I---GA-----M-S-R-----
BNL9	4k	TAA-LES--S-V-M-A--V-----I-X--GL-----M-SXQ-----
BNL10	4k	IGA-LES--S-V-VM-A--V-----I---GL-----M-S-R-----
BNL11	4l	LSA-LMSV---V-M-A--S-----GA-----M--Q-----
GB724	4x	VDA-LESF---V-M-A---V-----GA-----M--Q-----
BE95	5a	LGAVTAP---AV-Y-A-G-A-----A--AL-----M--YR--Q-A-
HK2	6a	AST---GF---V---A-A-VV--S-I-----L--A-----Q-----
FR1	7a	SSV-IHGF---V-----A-AF---M-I-----II-----R-KY-QV
VN4	8a	AST-V-GF-K-V-IM--A-AF---M-----GL-----LR--M-QV
VN12	9a	ASVSIRGV-E-V-----A-AF---M-----GL-----R--MYEI
NE98	10a	PCAATAS---T-V-MM-XA-----AL--X--G-SWRH-Q---

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Figure 2 - contin

TQGCNCSIYPGHITGHRMAWDMMMNWSPTTALVMAQLLRIPQAILDMIAG		
		301
HCV-1	1a	TQGCNCSIYPGHITGHRMA
HCV-J	1b	V-D-----VS-----
BNL1	1d	--E-----
BNL2	1d	--E-----
FR2	1f	V-D-----S-----XXX
HC-J6	2a	V-D-----T-----
HC-J8	2b	--E-----Q-----
CH610	2c	V-E-----X
NE92	2d	V-D-----
BNL3	2e	V-E-----
FR4	2f	V-E-----X
BNL4	2g	S-D-----
BNL5	2h	V-D-----
HCVTR	3b	V-T-----VS-----
GB116	4c	--D-----A--V-----
DK13	4d	--D-----T-----
CAM600	4e	--D-----T-----
GB809	4e	--D-----A-----
G22	4f	--E-----T-----
GB549	4g	--D-----D-----
GB438	4h	--D-----V-----
BNL7	4k	--D-----
BNL8	4k	A-D-----
BNL9	4k	--D-----
BNL9	4k	--D-----
BNL10	4k	--E-----
BNL11	4l	V-D-----
GB724	4x	--D-----T-----
BE95	5a	V-N-----S--V-----
HK2	6a	V-D-----T--V-----
FR1	7a	--D-----XNX--V-----
VN4	8a	V-E-----T-----
VN12	9a	A-D-----A-----
NE98	10a	V-D-----

FIG. 6A

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Isolate	Type	SEQ ID	core-V	100
			51	
			KT SERSQPRGRRQPIPKARRPEGRITWAGPYGPWPPLYGNEGCGWAGWLLSP-100	
HCV-1	1a		KT SERSQPRGRRQPIPKARRPEGRITWAGPYGPWPPLYGNEGCGWAGWLLSP	
HCV-J	1b		-----M-----	
BNL1	1d	2	-----X-X--S-----X-----	
BNL2	1d	6	-----D-----QSD-XX--H-----	
CAM1078	1e	10/60	-----E-----S-----X-----	
FR2	1f	12	-----S-----A-----	
FR16	1g	66	-----S--S-----M-----	
HCV6	2a		-----D--ST-KS-GK-----L-----	
HCV8	2b		-----D--ST-KS-GK-----L-----	
CH610	2c		-----D--TT-KS-GR-----L-----	
NE92	2d		-----D--T-KS-GK-----L-----	
BNL3	2e	14	-----D-XAT--S-GR-----L-----	
FR4	2f	18	-----D--AT-KS-GR-----L-----	
FR13	2k	76	-----D-X-Q-----D-XTT-KS-GR-----L-----	
EB1	3a		-----S--S-----	
NZL1	3a		-----S--S-----	
HCV-TR	3b		-----KQ-HL-----SR--S-----K--L-----	
GB358	4c		-----S--S-----	
DK13	4d		-----QL--S-----	
CAM600	4e		-----T--S-----	
GB809	4e		-----S--S-----	
BNL7	4k	28	-----S--S-----X-----	
HPCCOREEZA	4?		-----S--S-----F-----	
HPCCOREZB	4?		-----S--S-----	
HPCCOREZC	4?		-----S--S-----K-----	
GB724	4?		-----S--S-----A-----	
BE95	5a		-----Q-T--S-G-----A--L-----	
HK2	6a		-----Q-Q--H-----	
VN13	7a	46	-----V-HQT-----	
VN4	7c	44	-----V-HQT-----	
VN12	7d	48	-----A-----V-QNQ-----	
FR1	9a	42	-----V-Q-T--S-G-----	
NE98	10a	50	-----S-----R--T--S-----	
FR19	11a	104	-----V--TT-----	

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Isolate	Type	SEQ ID	150
			RGSRPSWGPTDPRRRSRNLGKVDTLTTCGFADLMGYIPLVGAPLGAARA
HCV1	1a	101	RGSRPSWGPTDPRRRSRNLGKVDTLTTCGFADLMGYIPLVGAPLGAARA
HCV-J	1b		
BNL1	1d	2	-----N----
BNL2	1d	6	-----
CAM1078	1e	10/60	-----X-----
FR2	1f	12	-----N-----S-T
FR16	1g	66	H-----S-----V-----
HC-J6	2a		N-----H-----V-----V-----
HC-J8	2b		T-----H-----R-----I-----V-----V-----
CH610	2c		-----H-----V-----V-----V-----
NE92	2d		-----H-----V-----V-----V-----
BNL3	2e	14/16	-----XX-----X-V-----V-X-----
FR4	2f	18	-----N-----H-----X-----V-----V-----
FR13	2k	76	-----H-----X-X-----V-----VX-V-----
HCV-TR	3b		-----N-----F-----V-----V-----
GB116	4c		-----N-----V-----V-----V-----
DK13	4d		-----X-X-----N-X-----V-----V-----
CAM600	4e		-----N-----N-----V-----V-----
GB809	4e		-----N-----N-----V-----V-----
G22	4f		-----V-----V-----V-----
GB549	4g		-----V-----V-----V-----
GB438	4h		-----V-----V-----V-----
BNL7	4k	28	-----N-----N-----G-I-----V-----
BE95	5a		-----N-----N-----K-----V-----V-A-----
HK2	6a		H-----N-----V-----V-----V-A-----
VN13	7a	46	X-----N-----X-----XX-----IE-----
VN4	7c	44	-----N-----N-----V-----X-----V-X-----
VN12	7d	48	-----D-X-N-----X-----E-----V-----V-AE-----
FR1	9a	42	-----N-----N-----XXL-----VL-G-----V-A-----
NE98	10a	50	-----N-----N-----

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Isolate	Type	SEQ ID
HCV1	1a	151
HCV-J	1b	200
BNL1	1d	4
BNL2	1d	8
FR2	1f	12
FR16	1g	66
HC-J6	2a	
HC-J8	2b	
CH610	2c	
S83	2c	
NE92	2d	
BNL3	2e	16
FR4	2f	18
BNL4	2g	20
BNL5	2h	24
BNL6	2i	26
FR13	2k	76
BR36	3a	
HCV-TR	3b	
Z4	4a	
GB809-4	4a	
Z1	4b	
GB116	4c	
GB215	4c	
GB358	4c	
DK13	4d	
CAM600	4e	
GB809-2	4e	
CAMG22	4f	
CAMG27	4f	
GB549	4g	
GB438	4h	
BNL7	4k	30
BNL8	4k	32
BNL9	4k	34
BNL10	4k	36

SUBSTITUTE SHEET (RULE 26)

LAHGVRVLE^TDGVNYATGNLPGCSFSIFLLALLSCLTVPASAYQVRNSTGL-200

151 200
 LAHGVRVLE^TDGVNYATGNLPGCSFSIFLLALLSCLTVPASAYQVRNSTGL
 -----I-----E--VS-I
 -----XT-HE--AS-V
 -----TT-HE--AS-V
 -X-----XG--XXXXX-X-XX--X-----T--E-HST-DG
 --Q-F-D-
 -----F-----I-T-V--AE-K-ISTG
 -----I-----V--V--VE--ISSS
 -----I-----S-----IS--V--VE-K-TSTS
 -----VE-KDTGDS
 -----I-----I--V-GL--K-TSSS
 -X-----I-X-----X-----V--V-XVE-K-TSQA
 -----I-----I--V--I--K-NSHF
 -----V--V--V--K-TSTM
 -----I-----V--K-TSHS
 -----I-----I--V--V--A-RS-S
 -----I-E-----S-----/I-X-V--VEIK-TXNT
 -----LEW--TS--
 -----A-G-----F--C--GLEYT-TS--
 -----EHY--AS-I
 -----EHY--AS-I
 -----VHY--AS-V
 -E-----AV--I-----S-----T--VNY--AS-V
 -----IHY--AS-V
 -----VNY--AS-I
 -----L-----NY--S-V
 -----AV--I-----T--VNY--AS-I
 -----AV--I-----GVNY--AS-V
 -----AV--I-----VHYH-TS-I
 -----VHYH-TS-I
 -----AV--I-----QHY--IS-I
 -----AV--I-----V--R-----QHY--AS-I
 -----I-F-----INY--VS-I
 -----I-----INY--TS-I
 -----I-----INYH-TS-I
 -----I-----I-X--X-----TNY--VS-I

BNL11	4k	38	--I--X-----	-----TNY--VS-I
BNL12	41	40	--I-----	-----QHY--VS-I
BE95	5a		-----I-----	-----VPY--AS-I
BE100	5a		-----I-----	-----VPY--AS-I
HK2	6a		---AI---I-----	-----LTYG--S--
VN4	7c	44	---XXI-X-X-XX-X-X-	-----T-----
VN12	7d	48	---AI---I-----	-----T-----
FR1	9a	42	---AI---I-----	-----T-----
NE98	10a	52	---I-F-----	-----F-----
				-----LT-TAGLEY--AS--

Isolate	Type	SEQ ID	V1	V2	V3	V4
			YHVTNDPCNSSIVYEADAAILHTPGCVPCVREGNASRCWVAMTPTVATRD			
HCV-1	1a	201	YHVTNDPCNSSIVYEADAAILHTPGCVPCVREGNASRCWVAMTPTVATRD			250
HCV-J	1b		S	M-M	S-F	L-L-A-N
BNL1	1d	4	S	I-MDGM-M-Y	D-HL	M-L-L-VKX
BNL2	1d	8	S	I-MSGM-A	N-S	MXL-L-VK-
FR2	1f	12	S-G	K-I-X-I	I-I	PL-L-A-I
HC-J6	2a		M	T-D-TWQLQA-V-V	EKV-T	IPVS-N-VQQ
HC-J8	2b		YA	S-N-TWQLT-V-L	ENDNGTLH	IQV-N-VKH
CH610	2c		M	S-WQLEG-V	E-QI	PVS-N-I-Q
S83	2c		MP	S-WQLEG-V	E-TA-V	PVA-NL-ISQ
NE92	2d		M	Q-WQLR-V-V	E-EK-I	IPVS-NI-VSQ
BNL3	2e	16	MA	S-N-WQLX-V-V	ENSSGRFH	IPIS-NI-VSK
FR4	2f	18	MA	A-D-WQLR-V-V	E-S-RTF	T-VS-N-VSR
BNL4	2g	20	MA	S-N-IWQM-Q-V-V	ELQ-K	IPV-N-VNQ
BNL5	2h	24	M	S-WQLK-V-V	E-HQ-Q	IPV-N-VSQ
BNL6	2i	26	M	S-WQLEE-V-V	EWKD-T	IPV-NI-VSQ
FR13	2k	76	M	S-X-TWQLXX-V-V	E-S	IPV-X-XVSR
BR36	3a		VL	S-D-V	I-QD-T-T	TPV-VKY
HCVTR	3b		VL	S-G-E-V-L	TT-Q-S	TTVST-V-T
Z4	4a		I	DHH-L	MT-T	TPV-VAH
GB809-4	4a		I	V-TDHH-L	A-V	TPV-AVS
Z1	4b		T	TEHH-M-L	TE-T	PL-APY
GB116	4c		I	DYH-L	V-Q	L-APY
GB215	4c		I	DHH-L	V-Q	LS-APY
GB358	4c		I	TEHH-L	V-Q	L-APY
DK13	4d		I	TDYH-L	K-T	SL-AQH
CAM600	4e		I	A-TENH-L	T-Q	L-SPY
GB809-2	4e		I	A-TDNH-L	KT-Q	L-SPY
CAMG22	4f		L	F-VHH-L	T-Q	L-L-APY
CAMG27	4f		I	F-EHH-L	T-Q	I-L-L-APH
GB549	4g		I	DHH-M-L	T-T	PL-APY
GB438	4h		I	DHH-M-L	T-V	IPL-VPY
BNL7	4k	30	Y	DHH-L	Q	L-APY
BNL8	4k	32	I	DHH-L	T-Q	L-APY
BNL9	4k	34	I	DHH-L	V-Q-S	L-I-APY
BNL10	4k	36	I	DHH-AL	V-Q	L-APY
BNL11	4k	38	I	F-DHH-L	K-H	L-APY

50/74

BNL12	41	40	-----SDHH-----L-----KT-----T-----L-----API
GB724	4x		-----I-----V-----TDHH-----L-----T-----V-----TPV-----AVS
BE95	5a		-----DNL-----A-----MT-----V-----QI-----LSAPS
BE100	5a		-----D-----L-----A-----KD-----V-----QI-----LSAPS
HK2	6a		-----L-----DAM-----L-----L-----VDDR-----T-----H-----V-----L-----IPN
VN4	7c	44	-----L-----ETL-----L-----KXX-----Q-----QAS-----L-----VPN
VN12	7d	48	-----L-----NGM-----L-----KT-----LTK-----LSAS-----L-----VQN
FR1	9a	42	-----L-----S-----N-----F-----ETM-----L-----IKA-----E-----LPVS-----L-----VPN
NE98	10a	52	-----M-----S-----G-----G-----I-----L-----S-----T-----IPVSX-----VKS

51/74

GKLPATQLRRHIDLLVGSATLCSALYVGDLCGSVFLVGQLFTFSPPRRHWT-300

Isolate	Type	SEQ ID	V4	V5
HCV-1	1a	251	GKLPATQLRRHIDLLVGSATLCSALYVGDLCGSVFLVGQLFTFSPPRRHWT	300
HCV-J	1b		SSI-T-TI-V-A-A-M-M-S	YE-
BNL1	1d	4	ASV-TXAI-V-XX-F-M-X-A	M-H-
BNL2	1d	8	ANV-TAAI-V-T-AFR-M	LYH-
FR2	1f	12	ANA-IDEV-V-A-VF-M-I-G	TS-
HC-J6	2a		PGALTQG-T-MV-M-G-M-AA-M-IV-QH-F	
HC-J8	2b		RGALTRS-T-V-MI-MA-A-V-A-MILS-A-MV-Q-NF	
CH610	2c		PGTLTKG-A-V-VI-M-V-ALMIAA-AVIA-Q-TF	
S83	2c		PGALTKG-A-II-M-V-V-ALM-AA-VVV-QH-TF	
NE92	2d		PGALTKG-T-TIIA-F-I-A-M-AS-V-II-QH-KF	
BNL3	2e	16	PGALTKG-AR-AV-M-V-A-MIAA-A-IVA-K-YE	
FR4	2f	18	PGALTRG-A-TI-M-I-A-MIAA-VAVV-QY-TF	
BNL4	2g	20	PGALTRG-T-TI-MV-I-V-A-MIAA-VVIV-QH-NF	
BNL5	2h	24	PGALTRG-T-TI-A-V-F-A-M-S-F-MI-QH-IF	
BNL6	2i	26	PGAXTKG-T-II-A-F	
FR13	2k	76	PGALTEG-S-TI-A-F-I-V-AIMIAA-VVIV-EH-HF	
BR36	3a		VGATTASI-S-V-A-M-M-A-A-R-Q	
HCVTR	3b		LGVTTASI-T-V-M-ARQ-AF-A-A-R-T	
Z4	4a		PGA-LESF-V-M-A-GA-M-MI-R	
GB809-4	4a		MDA-LESF-V-M-A-V-V-GA-M-Q	
Z1	4b		PNA-LESM-V-M-A-M-F-I-G-D-R	
GB116	4c		VGA-LES-S-V-M-A-V-I-G-M-S-Q	
GB215	4c		IGA-VESF-V-MM-A-V-I-G-M-S-R	
GB358	4c		IGA-LES-S-V-M-A-A-I-G-M-S-Q	
DK13	4d		LNA-LES-V-M-G-I-V-G-Q	
CAM600	4e		AGA-LEP-V-M-A-M-I-GL-M-Q	
GB809-2	4e		VGA-LEP-V-M-A-V-GL-M-Q	
CAMG22	4f		LGA-LESM-V-M-T-GL-A-M-R-L	
CAMG27	4f		IGA-LESM-V-M-T-GL-M-N-R-L	
GB549	4g		VGA-LESM-V-M-A-V-I-G-M-R	
GB438	4h		LGA-L-SV-Q-V-M-A-I-H-G-A-MVS-Q	
BNL7	4k	30	IGA-LES-S-V-M-A-V-I-X-XGL-M-S-R	
BNL8	4k	32	IGA-LES-S-V-M-A-V-I-GL-M-S-R	
BNL9	4k	34	IGA-LES-S-V-M-A-V-I-GL-M-S-R	
BNL10	4k	36	TAA-LES-S-V-M-A-V-I-X-GL-M-SXQ	
BNL11	4k	38	IGA-LES-S-V-VM-A-V-I-GL-M-S-R	

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BNL12	41	LSA-LMSV	V-M-A-S	GA	M-Q
GB724	4x	VDA-LESF	V-M-A-V	GA	M-Q
BE95	5a	LGAVTAP	AV-Y-A-G-A	A-AL	M-YR-Q-A
BE100	5a	FGAVTAP	AV-Y-G-A	A-AL	M-YR-Q-A
HK2	6a	AST-GF	V-A-A-VV-S-I	L-A	Q
VN4	7c	AST-V-GF-K-V-IM	A-AF-M	GL	LR-M-QV
VN12	7d	ASVSIRGV-E-V	A-AF-M	GL	R-MYEI
FR1	9a	SSV-IHGF	V-A-AF-M-I	II	R-KY-QV
NE98	10a	PCAATAS	T-V-MM-XA	AL-X-G-SWRH-Q	

V
TQGCNCSIYPGHI TGH RMA W D M M M N W S P T T A L Y M A Q L L R I P Q A I L D M I A G

Isolate	Type	SEQ ID	319
HCV-1	1a	301	TQGCNCSIYPGHI TGH RMA
HCV-J	1b		V-D-----VS-----
BNL1	1d	4	--E-----
BNL2	1d	8	--E-----
FR2	1f	12	V-D-----S-----XXX
HC-J6	2a		V-D-----T-----
HC-J8	2b		--E-----Q-----
CH610	2c		V-E-----X-----
S83	2c		V-E-----R-----
NE92	2d		V-D-----
BNL3	2e	16	V-E-----
FR4	2f	18	V-E-----X-----
BNL4	2g	20	S-D-----
BNL5	2h	24	V-D-----
FR13	2k	76	V-D-----P-X-----
BR36	3a		V-T-----L-----IS-----
HCVTR	3b		V-T-----VS-----
Z4	4a		--E-----T-----
GB809-4	4a		--D-----T-----
Z1	4b		--D-----VS-----
GB116	4c		--D-----A-V-----
GB215	4c		--D-----A-----G-----
GB358	4c		--D-----A-V-----
DK13	4d		--D-----T-----
CAM600	4e		--D-----T-----
GB809	4e		--D-----A-----
CAMG22	4f		--E-----T-----
CAMG27	4f		--E-----
GB549	4g		--D-----D-----
GB438	4h		--D-----V-----
BNL7	4k	30	--D-----
BNL8	4k	32	A-D-----
BNL9	4k	34	--D-----
BNL10	4k	36	--D-----
BNL11	4k	38	--E-----
BNL12	4l	40	V-D-----

GB724	4x	--D--	T--	--
BE95	5a	V-N--	S--	V--
BE100	5a	V-D--	S--	V--Q--
HK2	6a	V-D--	T--	V--
VN4	7c	V-E--	T--	--
VN12	7d	A-D--	A--	--
FR1	9a	--D--	XNX--	V--
NE98	10a	V-D--	--	--

44
48
42
52

69/74

FIG. 66B

VIPIDTTIMAKNEVFCVQPEKGGKPKRLIVFPDLGVRVCEKMALYDVT-2600
 KLPLAVMGSSYGFOYSPGQRVEFLVQAWKSKTIMGFSYDTRCFDSTVTE

Figure 6. NS5B amino acid alignment

Isolate	Type	SEQ ID	(G)
HCV-1	1a		2645 SDIRTEEAIIYQCCLDPQARVAIKSLTERLYVGGPLTNSRGCG 2694
HCV-J	1b		STVTESDIRTEEAIIYQCCLDPQARVAIKSLTERLYVGGPLTNSRGCG
2TY4	1c		N-----S-----A-E-Q-R-----K-Q-----
BNL1	1d	54	-----H-D-A-N-----K-----
BNL2	1d	56	-----N-V-S-----A-E-K-----I-X-----K-Q-----
FR17	1d	58	-----N-----XS-----AXE-K-----K-Q-----
CAM1078	1e	62	-----N-V-S-----A-E-K-----I-----K-Q-----
FR2	1f	64	-----A-----S-----H-E-----K-----K-----
FR16	1g	68	-----S-----S-----E-K-R-----I-----K-Q-----
HC-J6	2a		XX-----V-XS-----A-E-----K-Q-----
HC-J8	2b		-----R-----S-RA-S-PEE-HT-H-----MF-K-QT-----
ARG8	2c		-----R-----S-----A-S-PQE-TV-H-----M-K-QS-----
NE92	2d		-----R-----S-S-PEE-T-H-----M-K-QS-----
BNL3	2e	70	-----R-----S-LA-S-PE-T-H-----ML-K-QT-----
FR4	2f	72	-----R-X-----S-A-S-PE-T-H-----MM-K-QS-----
BNL5	2h	74	-----R-----S-LA-S-PE-T-H-----MM-K-QS-----
FR13	2k	78	-----A-R-----S-LA-S-PE-T-H-----MM-K-QS-----
FR18	2l	80	-----R-V-SV-LS-S-PEE-A-H-----MQ-K-QS-----
BR34	3a		-----R-N-S-FLA-S-PEE-TV-H-----I-MM-K-QS-----
BR36	3a		-----C-----MF-K-AQ-----
BR33	3a		-----C-----MF-K-AQ-----
T9	3b		-----C-----MF-K-AQ-----
PAK64	3g	82	-----H-----E-----E-E-K-SA-----I-MY-K-LQ-----
			-----Q-V-E-----E-E-R-----MF-K-LK-----

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GB48	4c	---K---V---EV---E-E-K-TA---MH-K-DL---	
GB116	4c	---K---V---EV---E-E-R-TA---MH---DL---	
GB215	4c	---K---V---EV---E-E-KV-TA---MH-K-DL---	
GB358	4c	---K---V---EV---E-E-K-TA---MH-K-DL---	
GB809	4e	---R---KV---EV---E-E-KV-AA---MH-K-DL---	
CAMG22	4f	---R---V---EV---E-ET-KV-SA---MH---DL---	
GB549	4g	---R---V---E---E-E-KV-SA---MY-K-DL---	
GB438	4h	---R---V---E---E-E-KV-SA-K---MY-K-DL---	
CAR4/120541		P---R-X-V-EV---N-EXDX-KV-NA---MH-K-DL---	
CAR1/501	4j	---X-R---GEV---E-E-KV-TA---MF-K-DL---	
EG13	4?	V---N-E-E-K-TA---MH-K-DL---	84
BNL8	4k	---K---P---EV---E-E-KV-TA---MH-K-DL---	86
BNL12	4l	---K---V---E---X-E-K-SA-X-L---MY-K-L---	88
EG81	4m	---R---V---EV---E-E-K-SA---MF-K-DL---	
BE95	5a	---H-M---S---S---Q-E-A-R-Q-C---MY-K-QQ---	90
CHR18	5a	---H-M---S---SLY-Q-E---R-Q-C---MY-K-QQ---	
VN13	7a	---R-VQ---HD---K-E-A-T-T-D-X---MX-K-QA---	92
VN4	7c	---R-X---HD---Q---V-K-T---CX-MM---QS---	94
VN12	7d	---S---R---HD---Q---V-K-T---C---MY---QS---	
FR1	9a	---GR---XD---LS-Q---E-K---MY-K-QL---	96
NE98	10a	---Q---V-LS-F-A---KDE-RV-T---C---MF-K-QH---	98
FR14	11a	---R---S---LS-Q-PEE-K---ME-K-QA---	100
FR15	11a	---R---S-XXA-Q-PEE-K---ME-K-QA---	102
FR19	11a	---R---S-XLA-Q-PEE-K---ME-K-QA---	106

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Isolate	Type	SEQ ID	YRRCR-2700
HCV-1	1a	2695	ASGVLTTSCGNTLCYIKARAACRAAGLQDCTMLVCGDDLWICE
HCV-J	1b		YRRCRASGVLTTSCGNTLCYIKARAACRAAGLQDCTMLVCGDDLWICE
2TY4	1c		-----L-T-----K-N-----
BNL1	1d	54	-----L-----R-----
BNL2	1d	56	-----L-----K-R-----
FR11	1d	58	-----L-----K-----
CAM1078	1e	62	-----L-----K-----
FR2	1f	64	-----L-----K-----
FR16	1g	68	-----L-A-----K-RE-----
HC-J6	2a		-----M-I-V-L-K-IIAP-----S-
HC-J8	2b		-----F-M-M-----L-K-IV-PV-----S-
ARG8	2c		-----A-M-----V-----N-IVAP-----
NE92	2d		-----F-M-I-V-Q-K-IIAP-----S-
BNL3	2e	70	-----H-----M-I-L-K-IVAP-----S-
FR4	2f	72	-----M-I-V-L-K-IVAP-----S-
BNL5	2h	74	-----M-I-V-L-K-IVAP-----I-S-
FR13	2k	78	-----M-----L-Q-IVAP-----S-
FR18	2l	80	-----F-M-I-V-M-IDAP-----S-
BR34	3a		-----P-F-I-T-A-RNPDE-----VA-
BR36	3a		-----P-F-I-T-AK-RSPDE-----VA-
BR33	3a		-----P-F-I-T-AK-RNPDE-----VA-
T9	3b		-----P-F-I-K-S-K-PSF-----VS-
PAK64	3g	82	-----P-Y-I-----A-PSF-----VA-

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GB48	4C	Y	F	L	S	IK	R	A
GB116	4C	Y	F	L	S	I	R	A
GB215	4C	Y	F	L	S	I	S	A
GB358	4C	Y	F	L	S	I	R	A
GB809	4e	Y	F	M	L	S	I	A
CAMG22	4f	Y	F	FL	T	TK	K	A
GB549	4g	Y	F	V	L	V	T	A
GB438	4h	Y	F	V	L	T	T	A
CAR4/120541		Y	F	L	T	T	K	A
CAR1/501	4j	Y	F	L	T	T	K	A
EG13	4?	F	F	L	T	T	K	S
BNL8	4k	F	F	L	T	I	R	
BNL12	4l	Y	F	L	S	I	R	A
EG81	4m	Y	F	V	L	T	T	A
BE95	5a	Y	F	L	T	T	K	A
CHR18	5a	F	M	M	L	S	R	A
VN13	5a	F	M	M	L	S	K	A
VN4	7a	ILA	L	L	Q	K	FD	S
VN12	7c	L	L	L	Q	K	KNYD	A
FR1	7d	F	L	M	L	Q	XK	KNFD
NE98	9a	P	M	I	FL	T	FT	YD
FR14	10a	P	F	I	K	TK	IKNPSF	A
FR15	11a	F	L	M	K	K	IV	PV
FR19	11a	F	L	M	X	KX	IV	PV
	11a	F	L	M	K	K	IV	PV

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SAGVQ

EDAAASLRAFTEAMTRYSAAPPQPPQPEYDLELITSCSSNVSAHDGAGKR-2800

Isolate	Type	SEQ ID	2745	2757
HCV-1	1a		SAGVQEDAASLRA	
HCV-J	1b		---T---A---	
BE90	1b		---T---V	
BNL1	1d	54	---E---N---	
BNL2	1d	56	---E---N---V	
FR17	1d	58	-X---E---N---V	
CAM1078	1e	62	-V-T-----	
FR2	1f	64	IE-XX--PS	
FR16	1g	68	-----	
HC-J6	2a		-Q-TE--ERN---	
HC-J8	2b		-Q-NE--ERN---	
NE92	2d		-Q-TE--ERN---	
BNL3	2e	70	-Q--E--DRN-	
FR4	2f	72	-Q-AE--ERN--V	
BNL5	2h	74	-Q-TE--ERN--V	
FR13	2k	78	-Q-TER-ENN--P	
FR18	2l	80	-Q-TE--ERN--V	
BR34	3a		-	
BR36	3a		-	
BR33	3a		-	
T9	3b		-C--E--R-A---	
PAK64	3g	82	-CX-D-EDRAALR	

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GB48	4C	-D--E--KRP-G-
GB116	4C	-D--E--KRA-G-
GB215	4C	-D--E--KRA-GV
GB358	4C	-D--E--KRA-G-
GB809	4e	-G--E--KRX-G-
CAMG22	4f	-D--E--RRA-G-
GB549	4g	-G--E--RA----
GB438	4h	-G--E--RA----
CAR4/12054i		-I-ID--KQA--T
CAR1/501 4j		-----E--PXTX-P
BNL8	4k	-D--E--NRA-X-
BNL12	4l	-E--E--SQP----
EG81	4m	-D--D--RRA-Q-
BE95	5a	-Q-TH--E-----
CHR18	5a	-Q-TH--K-----
VN13	7a	-L--S--TSA----
VN4	7c	-G--S--VDA----
VN12	7d	-G--P--GA--V
FR1	9a	-----N--I-N----
NE98	10a	-----ID--KSA----
FR14	11a	-K--E--QRD--V
FR15	11a	-K--E--QRD-
FR19	11a	-K--E--QRD--

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